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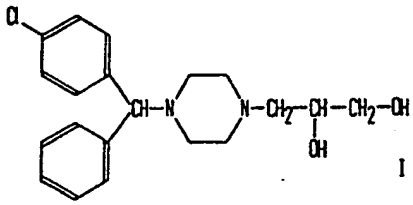
(54) **1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine**

(57) A new compound, 1-(4-chlorobenzhydryl)-4-(2,3-bishydroxypropyl) piperazine of formula



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and its addition salts with pharmaceutically acceptable organid and inorganic acids are disclosed, as well as pharmaceutical compositions containing same. The compound and such addition salts possess antitussive, antihistaminic, sedative, analgesic and antinflammatory utility.

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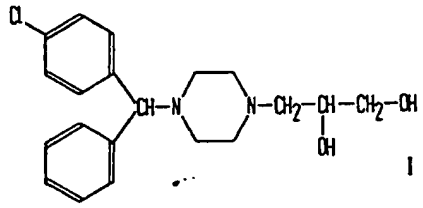
Certain of the Chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

A piperazine derivative and its use

A piperazine and its addition salts

The present invention relates to a new compound, namely 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine of formula



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as well as to its addition salts with pharmaceutically acceptable organic and inorganic acids. The compound possesses antitussive, antihistaminic, sedative, analgesic and antinflammatory utility.

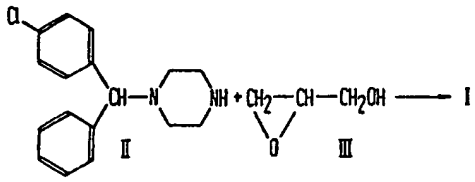
The invention also relates to the use of the compound of formula I as an antitussive, antihistaminic, sedative, analgesic and antinflammatory agent.

The invention further relates to pharmaceutical compositions containing the compound of formula I above or a salt thereof with a pharmaceutically acceptable organic or inorganic acid as the active ingredient in admixture with one or more of the usually employed pharmaceutical carriers.

Owing to the presence of the two basic nitrogen atoms, the compound of formula I above may form minor di-salts with either organic or inorganic acids. If a bi-functional acid is used, it is possible to obtain either acidic or neutral salts.

The compound of the invention can be prepared according to conventional procedures, which are briefly illustrated as follows:

a) 1-(4-chlorobenzhydryl)-piperazine is reacted with 2,3-epoxy-1-propanol according to this scheme



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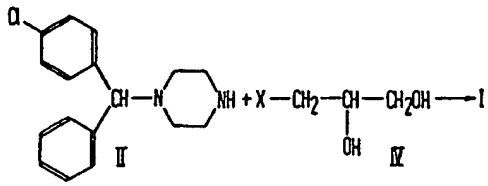
b) 1-(4-chlorobenzhydryl)-piperazine is reacted with a 3-halo-1,2-propanediol according to this scheme



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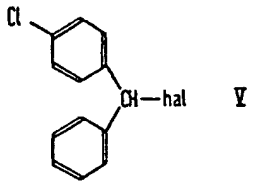
wherein X represents halo, preferably bromine or chlorine.

Piperazine derivatives have already been described, as an example in British Application 79/29842 of the same applicant. These compounds, however, did not display any antitussive action.

The starting 1-(4-chlorobenzylhydryl)-piperazine is mentioned in British Patent 817,231, U.S. Patent 2899436 and French Application 7303599, but its chemico- physical parameters as well as the process for its

preparation are not reported. We have found that this compound can be prepared by reacting a 4-chlorobenzhydryl-haide of formula



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wherein hal stands for a halogen atom, preferably bromine or chlorine, with piperazine, or a derivative thereof bearing on one of the two nitrogen atoms an easily removable group such as, for instance, 1-ethoxycarbonyl- or 1-benzylpiperazine.

As stated above, the compound of the invention possesses a remarkable antitussive utility as well as noticeable antihistaminic, sedative, analgesic and antinflammatory actions. These favorable biological properties are coupled with a low toxicity, as it results from the following table reporting the DL_{50} values of 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine and codeine used as the reference compound (the compound of the invention, may hereinafter be referred to as S-1498 and, where not specified, it is administered as the free base).

TABLE 1

Compound	LD_{50} mg/kg p.o. mice	LD_{50} mg/kg p.o. rats
S-1498	750	690
Codeine	405	515

p.o. = oral

These values are self-explanatory and confirm that compound S-1498 is considerably less toxic than codeine, a widely used antitussive medicament. They were determined according to Lichtfield and Wilcoxon, Journ. Pharm. Expt. Ther.,*96*,99,1949.

The antitussive action was investigated by means of several experiments carried out on guinea pigs, rats and cats.

In a representative experiment carried out on unanesthetized guinea pigs exposed to an aqueous 36 % citric aerosol, it was found that the present administration of S-1498 both by oral and intraperitoneal route was able to significantly inhibit the number of cough strokes in a predetermined time interval and that said inhibiting activity was statistically better than that of codeine. In the following table there are reported the results obtained by orally administering to the laboratory animals S-1498 and codeine at a dosage of 50 mg/kg 30 minutes before the exposure. The indicated percent variations were determined versus the controls i.e., unanesthetized guinea pigs administered only with physiological solution at an oral dosage of 5 ml/kg 30 minutes before the exposure.

TABLE 2

Controls		S-1498		Codeine	
progressive number of the animals	number of cough strokes in 10 minutes	progressive number of the animals	number of cough strokes in 10 minutes	progressive number of the animals	number of cough strokes in 10 minutes
1	36	1	10	1	7
2	24	2	8	2	16
3	26	3	7	3	12
4	32	4	10	4	15
5	31	5	11	5	9
6	35	6	9	6	24
7	27	7	17	7	22
8	34	8	13	8	12
9	36	9	10	9	25
10	30	10	9	10	20
11	28	11	11	11	16
12	34	12	10	12	11
M±s.d. 31,08 ± 1,18		M±s.d. 10.42 ± 0.74		M±s.d. 15.75 ± 1.71	
%Variation versus the controls		– 66,48		– 49.32	
P –		<,001		<,001	

M±s.d. = Mean±standard deviation.

The ED_{50} i.e., the dosage effective in causing a 50 % reduction of the cough strokes, was also determined which was 42 mg/kg both *per os* and by intraperitoneal route; under the same experimental conditions the ED_{50} of codeine as a free base was 55 mg/kg *per os*.

In a further experiment, an oral dosage of 40 mg/kg of S-1498 administered to rats thirty minutes before the exposure of the laboratory animals to a 10 % aqueous acetic acid aerosol was able to reduce, in a predetermined time interval, the cough strokes of about 56 % versus the controls, as it can be seen from the following table.

TABLE 3

Controls *		S-1498	
progressive number of the animals	number of cough strokes in 10 minutes	progressive number of the animals	number of cough strokes in 10 minutes
1	20	1	4
2	16	2	6
3	13	3	7
4	17	4	11
5	19	5	10
6	15	6	5
7	21	7	6
8	23	8	3
9	14	9	11
10	17	10	11
11	17	12	6
12	16	12	13
M±s.d.	17,33 ± 0,85	M±s.d.	7,67 ± 0,96
%Variation versus the controls	–		– 55,74
P	–	–	<,001

*Controls = rats administered only with physiologic solution by oral route at mg/kg thirty minutes before the exposure.
M±s.d. = Mean±standard deviation.

In a third representative experiment carried out substantially according to Domenjoz, Arch.Exp.Path.Pharmacol, *19*,215,1952 on the cat intravenously anesthetized with chloralose (75 mg/kg), it was found that a dosage of about 45 mg/kg of S-1498 administered by intraduodenal route caused a significant inhibition of about 62 % over the controls of the stimulation of the superior laringeal nerve. The same dosage administered through the same route to the anesthetized cat caused a % decrease of about 50 - 60 versus the controls of the cough strokes provoked by the mechanical stimulation of the trachea.

The antihistaminic activity of S-1498 was investigated by means of *in vitro* and *in vivo* experiments. In an *in vitro* test performed on guinea pig trachea rings according to Castillo and De Beer, J.Pharmacol., *90*, 104, 1947, the compound of the invention clearly showed a remarkable antagonist activity toward spasms by histamine and acetylcholine: ED_{50} values of 4 µg/ml and 16 µg/ml respectively were determined. An analogous degree of activity was also displayed against spasms by histamine and acetylcholine on the isolated guinea pig intestine. In an *in vivo* experiment on guinea pigs, S-1498 when administered either orally or intraperitoneally at a dosage of 60 mg/kg caused an almost total inhibition versus the controls of the bronchospasm induced by exposure to a histamine aerosol.

The obtained results are reported in Table 4: S-1498 was administered 30 minutes before the exposure and the "resistance time" indicates the time, in seconds, after which a bronchospasm is observed.

TABLE 4

Controls*		S-1498	
progressive number of the animals	resistance time	progressive number of the animals	resistance time
1	220	1	> 600
2	130	2	> 600
3	165	3	> 600
4	170	4	> 600
5	180	5	> 600
6	160	6	> 600
7	130	7	> 600
8	190	8	> 600
9	185	9	> 600
10	210	10	> 600
11	155	11	> 600
12	200	12	> 600
M±s.d.	174,58 ± 8,26		> 600
%Protec.	0		100

*Controls = guinea pigs administered with physiolagic solution by oral route at 5 ml/kg thirty minutes before exposure.
M±s.d. = Mean±standard deviation.

The sedative properties of S-1498 were evaluated on mice according to the behavioural scheme proposed by S. Irwin, Psychopharmacologia, Berl., *13* 222-257, 1968, taking into consideration the spontaneous motility as the indicative parameter. In this test the compound of the invention was administered to mice at an oral dosage of 100 mg/kg 30 minutes before starting the observation. The spontaneous motility of the laboratory animal was expressed as number of passages of the animal through a threshold in the laboratory apparatus in a predetermined time interval. The obtained results are summarized in the following Table 5. The controls were administered with physiologic solution at an oral dosage of 25 ml/kg.

TABLE 5

Controls		S-1498	
Progressive number of the animals	number of passages in 5 minutes	progressive number of the animals	number of passages in 5 minutes
1	43	1	24
2	51	2	33
3	53	3	34
4	45	4	14
5	60	5	34
6	42	6	28
7	45	7	31
8	55	8	17
9	61	9	14
10	50	10	38
11	43	11	33
12	41	12	39
13	51	13	29
14	53	14	17
15	63	15	22
16	49	16	8
M±s.d	50,31 ± 1,74		25,94 ± 2,39
%Variation versus the controls	–		– 48,44
P	–		<0.001

M±s.d. = Mean ± standard deviation.

The antiflammatory properties of S-1498 were evaluated by means of the carrageenin induced edema test, performed on rats substantially according to C.A.Winter et al., Proc.Soc.Exptl.Biol.Med., *111*, 544, 1962. In this experiment, the compound of the invention was orally administered to the laboratory animals at a dosage of 130 mg/kg 30 minutes before the injection in the hind paw of a carrageenin suspension. The volumes of the edemes were measured by a pletismograph. The controls received physiological solution at an oral dosage of 5 ml/kg together with the phlogistic agent. The obtained results are reported in the following Table 6.

TABLE 6

Controls				S-1498			
progressive number of the animals	volume of the edema (ml×100) after hours 1	2	3	progressive number of the animals	volume of the edema (ml×100) after hours 1	2	3
1	35	115	165	1	20	45	85
2	25	70	130	2	10	60	110
3	30	60	145	3	10	75	90
4	35	80	110	4	10	55	140
5	25	45	160	5	15	60	85
6	40	65	155	6	25	45	160
7	30	40	130	7	15	60	95
8	50	135	125	8	10	55	65
9	30	120	120	9	10	45	105
10	35	85	170	10	10	40	135
11	25	70	145	11	15	45	90
12	30	95	130	12	20	60	120
13	35	90	165	13	15	40	95
14	40	85	140	14	10	45	105
15	25	70	155	15	10	55	125
M±s.d.	32,67 ± 1,82	81,67 ± 6,88	143 ± 4,75		13,67 ±1,24	52,33 ±2,53	107,0 ± 6,17
%Variation versus the controls	–	–	–		– 58,16	– 35,93	– 25,17
P	–	–	–		<0.001	<0.001	<0.001

M±s.d. = Mean ± standard deviation

Finally, the analgesic activity of S-1498 was investigated by means of the writhing test, performed on mice as described by Koster et al., Fed.Proc. *18*, 412, 1959. The compound of the invention was tested at oral dosages of 50 and 100 mg/kg and was administered 30 minutes before the intraperitoneal administration of the writhes inducing agent i.e. 0.8% acetic acid, then it was measured the number of writhes in 15 minutes. The controls were administered with the writhes inducing agent and physiological solution at 25 ml/kg *per os*. The results are summarized in the following Table 7.

TABLE 7

Controls		S-1498 50 mg/kg		S-1498 100 mg/kg	
Progressive number of the animals	number of writhes in 15 minutes	progressive number of the animals	number of writhes in 15 minutes	progressive number of the animals	number of writhes in 15 minutes
1	52	1	4	1	6
2	48	2	11	2	6
3	40	3	29	3	10
4	34	4	32	4	11
5	28	5	17	5	9
6	29	6	9	7	10
7	30	7	10	7	8
8	33	8	18	8	10
9	28	9	11	9	9
10	31	10	17	10	10
11	30	11	21	11	11
12	35	12	12	12	10
13	29	13	20	13	6
M±s.d.	34,38 ± 2,15		16,23 ± 2,22		8,92 ± 0,51
%Variation versus the controls	–		– 52,79		– 74,05
P	–		<0.001		<0.001

M±s.d. = Mean ± standard deviation

Bearing in mind the peculiar pharmacodynamic activities of S-1498 as well as its low toxicity, the compound of the invention underwent also a chronic toxicity investigation on rats and dogs. S-1498 was administered to these animal species by oral route at dosages of 25 and 50 mg/kg/die for six months and it was found that such dosages were perfectly tolerated. Thus, a preliminary investigation in humans was carried out, whereby the compound of the invention was administered, at a daily dosage of 75 mg subdivided into three 25 mg doses, to twelve male and female patients, aging from 20 to 55 years, affected by irritative cough due to laringo-tracheitis or acute or chronical bronchitis. In all of the cases a complete disappearance or a significant diminution of cough was observed. In four patients affected by skin allergies the administration of S-1498 at the above indicated dosages led to a prompt recovery.

According to the present invention, S-1498 may be employed as the free base or in the form of the corresponding addition salts with pharmaceutically acceptable organic or inorganic acids. It may therefore be compounded into pharmaceutical dosage forms which can be used by oral, rectal, parenteral route and analogs. For the administration, the compound of the invention is embodied into solid or liquid pharmaceutical dosage forms. Representative examples of solid forms are tablets, capsules, powders, granules and sugar coated tablets. In these pharmaceutical forms, the active ingredient is mixed with the commonly employed pharmaceutical excipients such as, for instance, inert diluents, e.g. saccharose, lactose, starch and the like, and lubricants, e.g. magnesium stearate.

The liquid pharmaceutical compositions suitable for the oral administration are essentially represented by emulsions, solutions, suspensions, syrups, and elixirs. Such compositions contain the active ingredient in admixture with inert diluents, e.g. water or liquid petrolatum, and the usual emulsifying, coloring and flavouring agents. Furthermore, the pharmaceutical formulations suitable for parenteral administration are essentially aqueous or non aqueous sterile solutions, suspensions or emulsions; as the solvents or vehicles for such formulations propylene glycol, polyethylene glycol, vegetable oils like olive oil and/or the injectable organic esters such as, for instance, ethyl oleate, can advantageously be employed. The sterilization can be performed by various methods, as an example by means of a bacteriological filter, or by incorporating a sterilizing agent into the composition, or by irradiation or heating. The injectable pharmaceutical forms can also be prepared as solid sterile compositions to be solubilized before usage by means of sterile injectable liquids.

The common pharmaceutical compositions for rectal administration are suppositories containing, besides the active ingredient, cocoa butter or suitable waxes for suppositories as the excipients.

The following examples illustrate the invention in more detail but in no way may they be construed as a

limitation of the invention itself.

EXAMPLE 1

A) *1-(4-Chlorobenzhydryl)-4-ethoxycarbonyl-piperazine*

A mixture of 22.3 g (0.079 mole) of 4-chlorobenzhydryl-bromide, 12.51 g (0.079 mole) of N-ethoxycarbonyl-piperazine and 8.4 g (0.079 mole) of anhydrous sodium carbonate in 50 ml of anhydrous xylene was refluxed under stirring for 10 hours. After cooling to room temperature, the formed inorganic salts were filtered off and washed with anhydrous benzene. The washing liquids and the filtrate were collected and dried over sodium sulphate. After evaporation under reduced pressure an oily residue was obtained (28.2 grams, around 100% of theoretical). Thin layer chromatography (TLC) investigation of the obtained oily residue revealed a main spot with $R_f = 0.78$ (Merck F 254 silica gel plates; solvent: anhydrous ethyl acetate; visualization: U.V. light); the product was hydrolyzed without further purification.

B) *1-(4-Chlorobenzhydryl)-piperazine*

A solution of 120 g of potassium hydroxide and 28.1 g (0.079 mole) of the compound prepared under A) in 535 ml of 95% ethanol was refluxed for about 20 hours. After filtering and evaporating the solvent under reduced pressure, a residue was obtain, which was taken up with water and the resulting aqueous solution was extracted four times with 350 ml of diethyl ether (total diethyl ether = 1400 ml). The ether extracts were collected, washed with water, dried over potassium carbonate and evaporated; whereby 17.5 g (0.061 mole; 77.2 % over the 4-chlorobenzhydryl-bromide) of the title compound as an oily residue were obtained. Purity degree: 90-93% (titration with $HClO_4$).

C) *1-(4-Chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine*

5.0 Grams (0.017 mole) of the compound prepared under B) were dissolved in 7.6 ml of ethanol and the resulting solution was slowly added under stirring with a solution of 1.29 g (0.017 mole) of 2,3-epoxy-1-propanol in 3.6 ml of water at a temperature not exceeding 50°C. Stirring was continued for 7 hours at room temperature, then the solvent was removed by evaporation under reduced pressure and the obtained residue was twice taken up with anhydrous benzene: the benzene was each time evaporated in order to dehydrate the residue. The obtained raw product was subsequently taken up with a little absolute ethanol and the resulting mixture was added dropwise under stirring with an anhydrous ethanol solution of hydrogen chloride, thus causing the precipitation of 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine as the bis-hydro-chloride. Yield 4.2 g (57% of theoretical). M.p. 215-17°C (from absolute ethanol). An unitary spot with $R_f = 0.67$ was visualized by TLC.

Elemental analysis for $C_{20}H_{27}Cl_3N_2O_2$ (M.W. = 433.82)

	%C	%H	%N
Found	55.32	6.15	6.32
Calc.	55.37	6.27	6.46

Argentimetric titre of chloride ion : 100%.

EXAMPLE 2

A) 1-(4-Chlorobenzhydryl)-4-benzyl-piperazine

A mixture of 44.6 g (0.158 mole) of 4-chlorobenzhydryl-bromide, 27.85 g (0.158 mole) of 1-benzyl-piperazine and 21.85 g (0.158 mole) of anhydrous potassium carbonate in anhydrous xylene was refluxed for about 12 hours. After cooling to room temperature and filtering from any insoluble, the obtained filtrate was dried over sodium sulfate, then the solvent was evaporated off under reduced pressure. 58.9 Grams (99% of theoretical) of the title compound as a raw oily residue were obtained (purity degree: 92%; titration with $HClO_4$) which were used as such for the subsequent reaction step.

B) *1-(4-Chlorobenzhydryl)-piperazine*

6.0 Grams (0.016 mole) of the raw compound prepared under A) dissolved in ethanol were hydrogenated at 50°C and 3 atmospheres in the presence of 1.0 g of 10% palladium charcoal. The catalyst was removed by filtration, then the solvent was evaporated off under reduced pressure and a residue was obtained consisting of 3.03 g (66% of theoretical) of the raw title compound with a purity degree of 94% (titration $HClO_4$). The compound showed the same TLC pattern of that of the compound of Example 1 B).

C) *1-(4-Chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine*

2.8 Grams (0.01 mole) of the raw compound obtained under B was treated with 0.76 g (0.01 mole) of 2,3-epoxy-1-propanol substantially according to the same method as used in Example 1 C). 2.0 Grams (55% of theoretical) of raw 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine were obtained, as the free base, which were dissolved in a little absolute ethanol. The resulting solution was heated to 50-60°C and subsequently added dropwise under stirring with a hot alcoholic solution of maleic acid. Upon cooling, a

product separates which is 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine as the bis-hydrogenmaleate. M.p. 124-26°C (from absolute ethanol).
Elemental analysis for $C_{28}H_{33}ClN_2O_{10}$ (M.W. = 593.04)

	%C	%H	%N
Found	56.69	5.41	4.78
Calc.	56.71	5.61	4.72

EXAMPLE 3

A) *1-(4-Chlorobenzhydryl)-piperazine*

A solution of 3.5 g (0.04 mole) of anhydrous piperazine in 20 ml of toluene was added dropwise under stirring with 2.8 g (0.01 mole) of 4-chloro-benzhydryl-bromide. After refluxing the resulting mixture for 12 hours and subsequently cooling to room temperature, the formed piperazine hydrobromide was removed by filtration, the solvent was distilled off under reduced pressure and the obtained oily residue was distilled in vacuo. 1.35 Grams (48% of theoretical) of the fraction boiling at 231-34°C/10 mm.Hg were collected. The product can also be purified through a silica-gel column, by eluting with diethyl ether/light petroluem = 1/1 (V/V).

B) *1-(4-Chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine*

Treating the so obtained 1-(4-chlorobenzhydryl)-piperazine with 2,3-epoxy-1-propanol as described in Example 1 and 2, the 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine as the free base was obtained, which was added with a saturated alcoholic solution of picric acid. The corresponding dipicrate was readily obtained. M.p. 203-5°C (from absolute ethanol).
Elemental analysis for $C_{32}H_{31}ClN_8O_{16}$ (M.W. = 819.11)

	%C	%H	%N
Found	46.77	3.73	13.51
Calc.	46.92	3.81	13.68

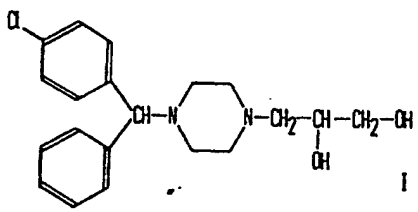
EXAMPLE 4

1-(4-Chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine

A mixture of 28.6 g (0.1 mole) of 1-(4-chlorobenzhydryl)-piperazine (prepared as illustrated in the above examples), 22.1 g (0.02 mole) of 3-chloro-1,2-propanediol and 10.1 g (0.1 mole) of triethylamine in 50 ml of anhydrous xylene was heated for 8 hours at 130°C. After cooling to room temperature the reaction mixture was added with 200 ml of anhydrous benzene and, after filtering from any insoluble, the filtrate was washed with water and a 10% aqueous solution of NaOH. The organic phase was subsequently dried over potassium carbonate, the solvent was evaporated off under reduced pressure and the obtained residue was heated *in vacuo* (50-60°C/0.1 mm.Hg) in order to remove the triethylamine. The so obtained 1-(4-chlorobenzyhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine as the free base was sufficiently pure for a subsequent salification, as reported in the preceding examples.

CLAIMS

1. The compound 1-(4-chlorobenzhydryl)-4-(2,3,bis-hydroxypropyl)-piperazine of formula



I

and its addition salts with pharmaceutically acceptable organic and inorganic acids.

2. The compound of claim 1 as the bis-hydrochloride.

3. The compound of claim 1 as the bis maleate.

4. The compound of claim 1 as the dipicrate.

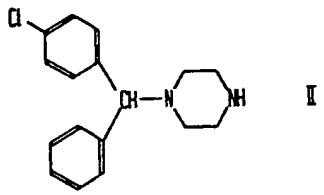
5. An antitussive, antihistaminic, sedative and antinflammatory pharmaceutical composition which contains as the active ingredient the 1-(4-chlorobenzyhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine of formula I or an addition salt thereof with a pharmaceutically acceptable organic or inorganic acid, in admixture with a conventional pharmaceutical carrier.

6. A pharmaceutical composition as defined in claim 5, which is suitable for oral administration.

7. A pharmaceutical composition as defined in claim 5, which is suitable for injectable administration.

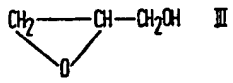
8. A pharmaceutical composition as defined in claim 5, which is suitable for rectal administration.

9. A process for preparing 1-(4-chlorobenzhydryl)-4-(2,3-bix-hydroxypropyl)-piperazine of formula I or an addition salt thereof with a pharmaceutically acceptable organic or inorganic acid, which comprises reacting 1-(4-chlorobenzhydryl)-piperazine of formula



II

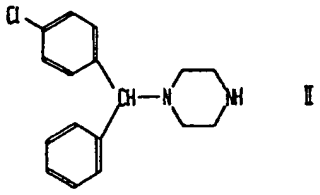
with 2,3-epoxy-1-propanol of formula



III

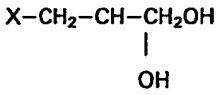
and, optionally, converting the obtained compound of formula I into a corresponding salt of a pharmaceutically acceptable organic or inorganic acid.

10. A process for preparing 1-(4-chlorobenzhydryl)-4-(2,3-bis-hydroxypropyl)-piperazine of formula I or an addition salt thereof with a pharmaceutically acceptable organic or inorganic acid, which comprises reacting 1-(4-chlorobenzhydryl)-piperazine of formula



II

with a 3-halo-1,2-propanediol of formula



IV

wherein X represents a halogen atom, and, optionally converting the obtained compound of formula into a corresponding salt of a pharmaceutically acceptable organic or inorganic acid.

11. A process according to claim 10, in which X in the 3-halo-1,2-propanediol of formula IV represents chlorine or bromine.

12. A process for preparing 1-(4-chlorobenzhydryl)-4-(2,4-bis-hydroxypropyl)-piperazine of formula I or an addition salt thereof with a pharmaceutically acceptable organic or inorganic acid conducted substantially as herein described and exemplified.

13. 1-(4-chlorobenzhydryl)-4-(2,3-bishydroxypropyl)-piperazine and addition salts thereof with pharmaceutically acceptable organic or inorganic acids whenever prepared by a process according to any one of claims 9 to 12.

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